DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

November 3,1999

CBER-00-004

WARNING LETTER

HAND DELIVERED

Andreas Gardi, Ph.D.
ZLB Central Laboratory
Blood Transfusion Service, Swiss Red Cross
Wankdorfstrasse 10
Postfach, 3000
Bern 22 Switzerland

Dear Dr. Gardi:

Inspections were conducted by the Food and Drug Administration (FDA) of the Central Laboratory of the Swiss Red Cross, Wankdorfstrasse 10, Bern, Switzerland, from June 9 to June 22, 1999, and from September 6 to September 10, 1999. During the inspections violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Part 211 were documented as follows:

1. Failure to conduct and fully document a thorough investigation of an unexplained discrepancy or the failure of a batch to meet its specifications or to extend the investigation to other batches that may have been associated with the specific failure or discrepancy [21CFR 211.192]. For example:

   a. deviation report [redacted] indicated that [redacted] lyophilized lot [redacted] had failed to meet visual inspection and maximum residual moisture specifications. The investigation stated that the lyophilization process parameters had been met and the action taken was to reprocess the lot. There was no investigation into the possible causes of the failure to meet the residual moisture and visual inspection specifications.

b. deviation report [redacted] reported black spots in vials of [redacted], lot [redacted]. The firm reprocessed the lot and released it for distribution as packaging lot [redacted]. There was no investigation into the identity and the possible sources of the black particles.

c. in 1998, four internal complaints reported that red spots had been observed inside the surface of vials from nine lots of [redacted] during the initial 100% visual inspection. The composition of the red spots was not analyzed in 1998. Data from an event that occurred in 1995 was used for the investigation, however, no testing was performed to verify that the events were similar. In addition, a toxicity assessment was not conducted before the lots were released for distribution.

d. [redacted] lot [redacted] failed the pyrogen test in 1995. The investigation was inadequate in that the conclusion that the lot was nonpyrogenic was based only on the nature of the fever reaction seen in the rabbits. Please be advised that USP 23 states that a temperature rise that occurs within three hours of injection must be considered in determining whether the test substance is pyrogenic. Anecdotal evidence that some rabbits show a quick response to pyrogenic materials cannot be the sole basis for invalidating pyrogen tests.

e. the failure investigation [redacted] for [redacted] lots which used stoppers that were contaminated with [redacted] was inadequate in that there was no evaluation of reserve samples for the presence of [redacted] and an analysis was not performed for the presence of [redacted] in final product.

2. Failure to establish procedures to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that reprocessing procedures for [redacted] and [redacted] have not been validated.

3. Failure to establish laboratory controls that shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures [21 CFR 211.160 (b)] in that scientifically sound sampling plans have not been established for the quantity of reserve samples and samples for lot release testing for [redacted] and [redacted].

4. Failure to establish time limits for the completion of each phase of production to assure the quality of the drug product [21 CFR 211.111] in that there is no data to support hold times for final [redacted] stored frozen in [redacted].

5. Failure to establish appropriate written procedures for the validation of a sterilization process to prevent microbiological contamination of product [21 CFR 211.113(b)] in that:

a. visual inspection personnel remove media filled bottles which are damaged or defective after the incubation period is completed. The turbidity status of the bottles is not always recorded in the batch record and the damaged or defective bottles are not sent to the Quality Control Microbiology Laboratory for evaluation prior to destruction.

b. there is no data to support the adequacy of the [redacted] day incubation period of the media filled bottles at [redacted]°C to allow for growth of molds, yeast, or fungi.

6. Failure to clean, maintain, and sanitize equipment at appropriate intervals to prevent malfunction or contamination that would alter safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67] in that there is no data to support the established maximum hold time of [redacted] days between the sterilization and use of lyophilizers.

7. Laboratory records do not always include complete data necessary to assure compliance with established specifications and standards [21 CFR 211.194(a)]. For example:

a. [redacted] 12 gram analysis [redacted] was documented to have been received on August 4, 1999, when in fact the sample was received on September 8, 1999.

b. [redacted] Lim[redacted] was documented to have been received on July 23, 1999, when in fact the sample had not yet been received in the laboratory.

8. Failure to establish a system for cleaning and disinfecting the room and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v)] in that equipment swabbing and percent recovery studies have not been performed for [redacted] based cleaning solution [redacted] for [redacted] cleaning of product contact equipment.

9. Failure to establish, maintain, and follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

a. there is no written procedure that states the maximum allowable time [redacted] is allowed to remain at room temperature during identification and accountability.

b. Standard Operating Procedure (SOP) A000002D, entitled "Deviation Control," was not followed in that a deviation report was not generated for

an operator error made during [redacted] of reprocessed [redacted] lot [redacted]

c. SOP Q100001D, entitled "Water Sampling," states that Water-for-Injection (WFI) samples for microbial and endotoxin testing are to be taken from [redacted] attached to the [redacted] However, the WFI samples are taken directly from the [redacted] during routine monitoring.

d. SOP Q100001D, entitled "Water Sampling," states that the [redacted] must be flushed for [redacted] minutes prior to sampling during routine monitoring for WFI. There are no instructions for operators to do the same during bulk production.

We acknowledge receipt of your written responses dated July 8, 1999; August 31, 1999; September 30, 1999; and October 27, 1999, to the Form FDA-483 issued at the close of the June inspection. We also acknowledge receipt of your written response dated October 1, 1999, to the Form FDA-483 issued at the close of the September inspection. We have reviewed your responses and find that they are inadequate to address our concerns and have the following specific comments to your responses, which are grouped according the inspection date and numbered to correspond to the observations listed on the Form FDA-483:

June 9 – June 22, 1999 inspection.

1. Your July 8, 1999, response indicates that your firm held and then [redacted] lot [redacted] due to a pyrogen test failure. The new [redacted] lot is [redacted] and is currently in [redacted] status. The [redacted] procedure included holding the final product for over [redacted] years and then [redacted] the [redacted] product, both of which are changes that may have an adverse effect on the identity, strength, quality, purity, or potency of the product. Before the [redacted] product may be distributed you must submit a prior approval supplement to FDA's Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review (OBRR) pursuant to 21 CFR 601.12(b).

3. Please be aware that the validation of [redacted] procedures for [redacted] must be submitted as a prior approval supplement to CBER's OBRR pursuant to 21 CFR 601.12(b). In addition, the review and approval of [redacted] procedures for [redacted] will be handled by CBER's OBRR through Reference Number 97-0739.

12. The failure investigation report for the black particles in [redacted] lot [redacted] submitted in the September 30, 1999, response does not indicate possible sources of the contamination.

13. Your response dated July 8, 1999, indicates that an identical problem with the supplier of [redacted] occurred in 1995. The response does not indicate what

actions will be taken in reference to the supplier to assure that the problem with the red spots will not occur a third time.

September 6 – 10, 1999 inspection.

6. Please provide a rationale for the implementation date of January 31, 2000 for the controlled worksheet procedure. Please provide interim measures that will be taken to assure the accountability of all worksheets. In addition, please provide interim measures that will be taken to assure the accountability of samples for Quality Control testing until the implementation date of December 31, 1999, for the new procedure.

12. Your response states that a task force reached the conclusion that the [redacted] lots contaminated with [redacted] were not considered a health hazard. Please provide an English translation of the medical and toxicological information that the task force used to come to this conclusion. In addition, please provide a list of the affected final product [redacted] lots and their disposition and the number of stoppers affected by this contamination.

Neither the above violations nor the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspections are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension and/or revocation, and/or import alert, which would prevent your product from entering the United States. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

You should respond to FDA in writing within 15 working days of receipt of this letter of the specific steps you have taken to correct the noted violations and to prevent their recurrence. Corrective actions addressed in your previous letters may be referenced in response to this letter, as appropriate. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. FDA will verify your implementation of promised corrective action during the next inspection of your facility. Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case

Management, HFM-610. If you have any questions regarding this letter, please contact Annette Ragosta at (301) 827-6322.

Sincerely,

Deborah D. Ralston
Acting Director
Office of Regional Operations